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<p>Thus far, studies on Gulf War veterans have not defined any syndrome specific to deployed Gulf War veterans, but have only suggested that Persian Gulf War veterans have a higher frequency of a number of symptoms compared to non-deployed veterans. We have expanded on the factor analysis approach used by other investigators and have found one factor with four symptoms that suggests a syndrome unique to deployed Gulf War veterans. Each of the symptoms (blurred vision, tremors, speech difficulty, and ataxia/dizziness) is subject to verification by clinical examination. We propose to perform detailed neurological evaluations of a sample of Persian Gulf War veterans and three control groups: a sample of Gulf War veterans with post-traumatic stress disorder and reporting none of the four symptoms; non-Gulf War veterans reporting all four of the symptoms (only 0.46% of the non-Gulf War veterans); and a random sample of Gulf War veterans reporting none of the four symptoms. Detailed information on potential risk factors will be collected on all participants. In addition, blood samples will be obtained from the study participants to allow further studies if a new clinical syndrome with objective neurologic abnormalities are identified in this study.</p>			
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## **Annual Report Gulf War Project (Revised)**

May 31, 2001

### **Introduction**

To date, no study has demonstrated conclusively that "Gulf War Syndrome" (GWS) is related to deployment in the Gulf War. While it is clear that veterans who served in the Gulf War returned with illnesses, including chronic fatigue syndrome and post-traumatic stress disorder, there currently is no proof that these illnesses are associated with a deployment-related syndrome. In the case of both of these illnesses, non-deployed service persons have also exhibited symptoms, albeit to a lesser degree.

However, a factor analysis we recently conducted and is now in press in the Archives of Environmental Health (**attached**) identified a "factor," or cluster of symptoms found only in groups of veterans deployed in the Gulf War. Some symptoms in this cluster include blurred vision, speech difficulty, hand tremor, and instability.

The purpose of the project supported by this grant is to determine whether anything objective can be identified on a medical-neurological work-up that will indicate that the cluster of symptoms experienced by deployed veterans is indeed a syndrome. To this end, four representative groups of patients will be examined over a period of 2 ½ years. An experimental group comprising deployed veterans exhibiting the cluster of symptom, a control group of veterans with post-traumatic stress disorder, a control group of veterans who were not deployed but exhibit similar signs and symptoms of the syndrome, and a control group of randomly selected veterans.

### **Hypotheses**

The study will evaluate the following research hypotheses as stated in the original proposal.

1. Gulf War veterans who are suspected cases (report all of the four symptoms) will have a higher rate of confirmation (meaning objectively identified physical abnormalities) of their symptoms (confirmed cases) than non-GW veterans who are report all of the four symptoms.
2. Gulf War veterans who are suspected cases will have a higher rate of abnormal neurologic findings than Gulf War veterans who are not suspected cases (report none of the four symptoms).
3. Gulf War veterans who are suspected cases will have a higher rate of abnormal neurologic findings than Gulf War veterans with suspected Post-Traumatic Stress Disorder.
4. Gulf War veterans who are suspected cases will have a higher rate of exposure to environmental hazards and psychological stressors than non-cases.

### **Phase 1**

The tasks listed under Phase 1 have been successfully accomplished. Dr. Ladan Zolfghari, a physician with experience in Gulf War related issues, was recruited as the clinical coordinator and has proven to be an effective co-coordinator. The multiple financial issues that have developed associated with this project have required the recruitment of a financial coordinator as well and we have been fortunate to identify a

talented financial coordinator, Ms. Shari Thompson, who is also experienced in DoD procedures and clinical research. She is responsible for many administrative tasks and, in addition, performs all SCID interviews.

Among the other accomplishments in this phase are the design of case report forms and a study database, obtaining IRB approval at The George Washington University and negotiating wording changes on Informed Consent between GW and DoD. As suggested by DoD, we recruited a medical monitor for adverse events and following the experience of Dr. Kang, our co-investigator in the Dept. of Veterans Affairs, we have assembled an Advisory Board from experts in the areas of neurology, psychiatry, epidemiology and veterans' affairs. This Advisory Board has met with us once early in the study and gave us extremely useful suggestions.

The major problem we encountered in this initial phase was the administrative difficulties between DoD and the VA, which delayed the initiation of recruitment of subjects by several months. Initially planned as an interagency agreement, the delay in completing this agreement resulted in funds not being available in time for the VA to use before the end of their fiscal year, and therefore we had to begin anew getting the funds to the VA via a subcontract. These obstacles were overcome, however, and we were able to enter several local subjects who did not require plane fare and therefore the starting date of the clinical evaluation was not delayed as long as it could have been.

## Phase 2

The recruitment and work-up of subjects has gone very smoothly. The VA has identified 180 potential subjects for initial recruitment, assuming that we should be able to recruit the 90 proposed for study out of this pool. As of Jan. 31 we have sent recruitment letters to 80 of the subjects and thus far 35 have agreed to participate in the study. Of the first 23 scheduled, the examination was completed on 15. Of the 15 subjects examined thus far, 53% were male, 46% were white, 31% were black, and the average age was 43.5 years. We have concentrated on bringing in subjects with the putative neurological syndrome and therefore of these 15, 6 were in our primary study group and the other 3 study groups have had 3 participants in each.

The George Washington University staff is blinded as to which study group the subjects are enrolled. It is impossible to describe whether the symptoms occurring in those enrolled are consistent with their designation to the four study groups. Group 1 consists of deployed veterans with the putative syndrome. Group 2 consists of non-deployed veterans who have some of the same symptoms. Group 3 consists of deployed veterans with symptoms indicative of post-traumatic stress disorder, and Group 4 consists of randomly selected deployed veterans who have none of the four symptoms comprising our suspected new syndrome. We do know, however, that there is a sizeable proportion of symptomatic veterans as well as many with no symptoms suggestive of an illness, and therefore the selection criteria appear to have been appropriate. It is also apparent that we have subjects with evidence of PTSD by current questionnaires and interviews (Mississippi and SCID), and subjects with objective findings (ENG abnormalities, visual field abnormalities, early cataracts, etc.). An independent satisfaction survey form the department of Veterans Affairs indicated general satisfaction with travel arrangements; accommodations, and evaluations.

Subsequent actions by the study team addressed the two major concerns noted by the subjects: discomfort with the ENG (one subject) and inadvertent billing by business office. Attention is being given to all concerns noted on the survey. Exit interviews on the first seven subjects indicated that they were pleased with their evaluations at The George Washington University Medical Center, believed their trip and participation were very worthwhile, and look forward to hearing the outcome of the study a year from now.

## Methods

All participants are being recruited from veterans participating in the National Health Survey of Persian Gulf War Era Veterans. The sample sizes available for each group, along with the number we expect to contact for participation and the final sample sizes undergoing the testing are shown below. Based on past experience, we anticipate that about 50% of veterans on the contact list will be available and will participate. All contact lists are generated using simple random sampling. In order to reduce travel costs, groups 1, 3, and 4 are selected primarily from the Mid-Atlantic Region. If recruitment rates fall below 50%, we plan to sample additional veterans to be contacted. There is a small possibility that limiting selection to available veterans within a specific geographic region will introduce some selection bias as those veterans who are not available may still be enlisted in the military or on active duty and thus may be healthier.

Group Name	Available Pool from VA PG Survey		Tentative Sample Size to be contacted	Final Sample
	Total	Residing Mid-Atlantic Region		
1-PGW-SC	277	36	60	30
2-NonPGW-SC	43	19 (East Coast)	40	20
3-PGW-PTSD	215	33	40	20
4-PGW-Normal	6730	477	40	20

As stated in the proposal, a physical and neurological examination is performed on each veteran. The neurological examination consists of assessment of mental status and speech, cranial nerves, motor function in the arms and legs, light touch, pinprick, vibration and joint position sensation, coordination, gait and deep tendon reflexes. Particular attention is paid to the observation of speech difficulty and tremors during the physical and neurological examinations. Evaluation of blurred vision is performed by an ophthalmological examination performed and includes visual acuity, visual fields, eye movement and strabismus evaluations, and glaucoma testing. Visual evoked response (VER) testing, which evaluates the conduction through the central nervous system optic pathways from the optic nerve to the occipital cortex, is also performed on all veterans. Electronystagmography (ENG), brain stem evoked response (BAER) and somatosensory evoked potentials (SSEP) are being performed per the original proposal to evaluate problems with loss of balance/dizziness. Electroencephalograms (EEGs) are also performed on all veterans as part of this testing battery to assess the reports of

## **APPENDIX A**

### **Evidence for a Deployment Related Gulf War Syndrome by Factor Analysis**

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## ABSTRACT

To identify a syndrome unique to Gulf War veterans, an exploratory factor analysis was applied to the 47-symptom correlation matrix of 10,423 Gulf and 8,960 non-Gulf veterans who participated in a population based health survey. A separate factor analysis was performed for Gulf and non-Gulf veterans and the resulting six factors were compared between the two groups. Five of the factors were very similar in the two groups. However, one of the factors in the Gulf group, but not the non-Gulf group, contained a cluster of symptoms consistent with neurological impairment. Symptoms specific to this factor were blurred vision, loss of balance/dizziness, tremors/shaking and speech difficulty. The Gulf veterans who had all of those symptoms (N=277) also reported exposures to several putative risk factors at a rate three or more times higher than other Gulf veterans. This finding suggests a possible syndrome related to Gulf War deployment, which requires objective supporting clinical evidence.

## I. INTRODUCTION

The health consequences of the 1990-91 Gulf War on veterans have been the focus of many reports and studies since the war.<sup>1-6</sup> Numerous studies have documented that Gulf War veterans reported symptoms and debilitating health problems significantly more often than their non deployed military peers. However, many of these Gulf War veterans have received no diagnosis that explains their symptoms. Most common symptoms reported by Gulf War veterans included fatigue, muscle/joint pain, headache, memory loss, sleep disturbance, rash and difficulty concentrating.<sup>7-8</sup> Several possible etiologic agents for the symptoms reported by Gulf War veterans have been suggested which include exposure to multiple vaccines, pyridostigmine bromide, toxic chemicals, chemical and biological warfare agents and depleted uranium as well as stress associated with battle field conditions and rapid deployment and redeployment.<sup>9-13</sup>

There have been several important studies to determine whether the pattern of symptom reporting by Gulf veterans differs from that of non-deployed veterans. Factor analysis was used to identify a cluster of symptoms and syndromes unique to Gulf War veterans. Basically, factor analysis is a statistical technique used to understand patterns of correlation in observed variables.<sup>14</sup> The primary output of factor analysis is a set of factors and coefficients that estimate the strength of association of each variable with these factors. Factors are generated through mathematical operations on the correlation matrix. A factor represents a group of variables intercorrelated with each other but relatively uncorrelated with other variables.

Haley et al. were the first group to apply factor analysis to a Gulf War veterans' health study, in which an exploratory factor analysis of 52 symptoms in 249 Gulf War veterans from a Naval reserve construction battalion was conducted.<sup>15</sup> Six factors, which accounted for 71% of the total variance of the observed variables were identified and reported as evidence for a unique Gulf War syndrome. It is important to note that the observation is based on a single Naval unit of Gulf veterans without a non-deployed comparison group. Furthermore, a small number of participants and a low participation rate (41%) hinders generalizability to other Gulf War veterans.

Fukuda et al. reported an exploratory factor analysis result of 35 symptoms from a larger sample of 3,723 Air Force, Air Force Reserve and Air National Guard veterans who were still in the military at the time of the survey.<sup>16</sup> The exploratory factor analysis originally identified 10 possible factors, but confirmatory analysis yielded two factors, mood-cognition-fatigue and musculoskeletal. A total of 10 symptoms are included in these two factors. Based on the factor analysis results and their clinical experience, a case was defined as someone who had one or more chronic symptoms from at least two of the following three categories: fatigue, mood – cognition, and musculoskeletal. Although a significantly higher proportion of Gulf War veterans met the case criteria (39%), approximately 14% of non Gulf War veterans also met the same criteria. They concluded that the chronic multisymptom condition was not associated with specific Gulf War exposure and also affected non-deployed military personnel. The finding was based on Air Force personnel who were still on active duty several years after the war. Therefore, it may be difficult to generalize to individuals who served in other branches of service or those who left the military service.

Ismail et al. analyzed symptom data collected from a population based cross-sectional survey of three United Kingdom military cohorts: Gulf veterans cohort, Bosnia cohort and non-deployed era cohort.<sup>17</sup> Three factors, mood cognition, respiratory system and peripheral nervous system, which accounted for about 20% of the variance in British Gulf veterans were identified. The frequency of symptom reporting was higher among the Gulf War veterans. However, the underlying structure of the correlation between symptoms (factors) was similar to that in the Bosnia cohort and era cohort, which seems to suggest evidence against the existence of a unique Gulf War syndrome.

To identify a cluster of symptoms unique to Gulf War veterans, we also performed a factor analysis of symptoms similar to those previously reported but on 1) a population-based sample of 2) a much larger cohort of 15,000 Gulf War veterans and 15,000 non-Gulf War veterans 3) separately. Both male and female troops, those who remained on active duty and those who were separated from the military, those who served in each of the four military branches and those who were assigned to each of the three unit components (regular, reserve, National Guard unit) were all represented in the sample.

## II. METHODS

### Study Population

The study population consisted of a population based sample of 15,000 Gulf War veterans and 15,000 non-Gulf War veterans. In this study, the term "veteran" referred to any individual who served on active duty or in the reserves or National Guard during the period of the Gulf War, irrespective of whether they were still in service or separated

from the military. A stratified random sampling method was adopted to ensure that each subgroup of deployed military personnel was adequately represented in the sample. The Defense Manpower Data Center (DMDC) provided a roster of 693,826 U.S. troops who were deployed to the Persian Gulf area during the Gulf War. This population was stratified by gender, unit component (regular, reserve and National Guard), and branch of service. Women and those who served in reserve/National Guard units were oversampled to result in  $\frac{1}{5}$  of the sample to be women, about  $\frac{1}{4}$  National Guards and  $\frac{1}{3}$  reservists. Similarly, the population of 800,680 non-deployed troops identified by DMDC were stratified by gender, unit component, and branch of service. From each strata, a requisite number of troops were randomly selected to mirror the number in the same strata in the Gulf War deployed troops. The final distribution of Gulf War veterans and non-Gulf War veterans by the selection criteria are listed in Table 1.

### Survey Design

In phase I of the survey, a structured health questionnaire was mailed to each of the 30,000 Gulf War-era veterans. Up to four follow-up mailings were sent to non-respondents to increase the response rate. In Phase II, a follow-up telephone health interview was attempted on all non-respondents using the same questionnaire. Information collected from veterans included: presence of various symptoms, medical and psychological conditions, exposure in the Gulf theater, self assessed health status, functional impairment, history of clinic visit and hospitalization, life events checklist, PTSD (posttraumatic stress disorder) Checklist,<sup>18,19</sup> smoking and alcohol use, and

pregnancy outcomes including birth defects. A self-reported symptom checklist comprised of 48 items, which were representative of the symptoms configuration commonly observed among Gulf War veterans and civilian outpatients, was used to assess the prevalence of somatic and psychological symptoms.<sup>20</sup> Information on the time of onset and severity of symptoms was also collected.

### Statistical Analysis

A factor analysis is a useful statistical tool for a variable reduction procedure when one has data on a large number of variables (e.g., 47 symptoms) and there appears to be some redundancy in those variables. In this survey, redundancy means that some of the symptoms are correlated with one another, possibly because they are measuring the same construct. By a factor analysis, it is possible to reduce the observed 47 symptom variables into a smaller number of factors (artificial variables) that will account for most of the variance in the observed variables.

Two exploratory factor analyses of the 47 symptoms (one question pertained only to males was deleted) were performed separately in the Persian Gulf ( $n=10,423$ ) and non-Persian Gulf ( $n=8,960$ ) veteran groups to assess whether there exists one or more factor(s) structures underlying this set of symptoms in each of the two survey populations. Those participants with incomplete symptom data were excluded from the factor analysis.

There are essentially three major steps involved in performing a factor analysis which are almost universally applied: choosing one of the mathematically available methods for extracting factors from the correlations among items (symptoms); choosing

the meaningful number of factors; and choosing a mathematically defined method for "rotating" the factors to make them more interpretable. In this study we use the "iterated principal factor analysis" method. Here, the first factor extracted accounts for the largest degree of correlation among symptoms. Successive factors are extracted from what remains in the correlation matrix after correlation due to the previous factors has been removed. The process of rotating the initially extracted factors serves to sharpen the distinction among the extracted factors. The promax method chosen here allows the resulting factors to be uncorrelated.

A scree plot, which is a graphical method for determining the number of factors, was used to suggest the initial number of factors to retain for rotation. However, because there is no absolute method for determining the number of meaningful factors, we augmented the initial analysis by examining the findings, especially factor interpretability, with varying numbers of factors rotated. This approach to determining the number of factors introduces a subjective component, but is consistent with recommendations by contemporary factor analysis methodologists.<sup>21,22</sup> In addition, sensitivity analyses were performed to test how sensitive the results of the factor analysis were to the use of the sampling weights and different symptom severity coding systems. The methods chosen here for all three steps of the factor analysis are widely used and recommended.<sup>23,24</sup> Symptoms considered relevant to a factor were those which had factor loadings greater than 0.3, a common criterion for deciding whether a variable is "salient" or meaningful for describing a factor. All extracted rotated factors had at least 2 symptoms with loadings above 0.4. Chi-square tests of significance were conducted on the data in Tables 2,4, and 5.<sup>25</sup>

### III. RESULTS

#### Survey Participants and Their Characteristics

A total of 20,917 veterans completed the survey questionnaire resulting in the overall response rate of 70%. After reclassification of Gulf War deployment status based on self-reported service history, the final count for Gulf War veterans was 15,225 of which 11,441 responded (75.1%); and for the non-Gulf veterans, 14,775 of which 9,476 responded (64.1%). No significant difference ( $p>.01$ ) was found between survey participants and non-participants with respect to gender. The differences by branch of service and unit component, although statistically significant because of the large sample sizes, were not substantially meaningful. In both Gulf War veterans and non-Gulf War veterans, non-participants were more likely to be younger, minority, unmarried individuals who served in enlisted ranks at the time of the Gulf War (Table 2).

In evaluating self perceived general health status (excellent, very good, good, fair, poor), the health status of veterans who responded earlier in the survey did not differ from the veterans responding toward the end of survey period. Likewise, based on the telephone survey of non-respondents, it did not appear that self-perceived exposure to harmful conditions in the theater influenced significantly whether they would participate or not. There appeared to be little evidence for non-respondent bias with respect to exposure or outcome.

The mean age of participants in 1991 was 31 years;  $\frac{1}{5}$  were women;  $\frac{3}{4}$  were white;  $\frac{1}{2}$  were married at the time of Gulf War; over 83% served in enlisted ranks during the War; and less than 20% remained on active duty at the time of survey. All branches

of service (Air Force, Army, Marine, Navy) and all three military unit components (regular, reserve, National Guard unit) were represented in the survey.

### Factor Analysis

Initially, four factors were extracted. The first step of our sensitivity analysis was to determine whether the sampling weights would have an important impact on the results for these four factors. The pattern of factor loadings was very similar when comparing analyses with and without sampling weights applied. Since the results were very similar, the sampling weights were used for all further analyses. The next step was to determine whether the symptom coding system (0=None; 1=Mild; 2=Severe) had an important impact on the factor loadings for the four factors. The symptom coding was collapsed to None/Mild (=1) vs. Severe (=2). The symptom coding system was found to have little impact on factor loadings. All further analyses were therefore done with the uncollapsed symptom coding system (0=None; 1=Mild; 2=Severe) so as to make maximal use of the data.

The four factor solution did not yield readily interpretable factors, but there seemed to be a respiratory/infectious group of symptoms, a gastrointestinal grouping, a musculoskeletal grouping, and a factor that included a combination of neurological, fatigue and mood symptoms.

In factor analysis an "eigenvalue" represents the estimated variance of a factor. The eigenvalues (and proportion of variance explained) for the first 6 factors before rotation were as follows for the Gulf group: 12.82 (0.79), 1.27 (0.08), 0.92 (0.06), 0.78 (0.05), 0.68 (0.04), and 0.53 (0.03). Similarly, the eigenvalues (and proportion of

variance explained) for the first 6 factors before rotation for the non-deployed group were 10.39 (0.71), 1.39 (0.10), 1.02 (0.07), 0.99 (0.07), 0.72 (0.05), and 0.57 (0.04). Sometimes there is a point in the sequence of eigenvalues where there is a sharp drop and this can help in choosing the number of factors to retain. Examination of the eigenvalues yielded no clear break point that could be used to strongly determine the number of factors; therefore, analyses extracting five and six factors were conducted. The five factor solution was similar to the four factor solution with the sore throat, trouble swallowing and swollen glands symptoms now forming their own factor as opposed to grouping with the respiratory symptoms as they had in the four factor analysis. The Gulf and non-Gulf veterans still displayed virtually identical factor solutions. Factor interpretability suggested that the six factor solution was more appropriate.

The six-factor solution produced different results for the Gulf and non-Gulf veterans. Five of the factors were of similar composition in both the Gulf and non-Gulf veterans (Table 3). The order of the factors was the same except for the presence of a neurologic factor in the Gulf veterans which did not have a parallel factor in the non-Gulf veterans; therefore, for the purpose of this paper the factors will be numbered according to their ordering in the Gulf veterans. While the Gulf veterans group showed evidence of the presence of a neurological factor, the second factor in the non-Gulf group included two fatigue symptoms that loaded on Factor 1 in the Gulf veterans. This neurological factor, present in the Gulf veterans, contained a cluster of symptoms that did not load on any of the factors in the non-Gulf veterans. This cluster of symptoms was blurred vision, loss of balance/dizziness, tremors/shaking, and speech difficulty. The factor also contained two other symptoms (concentration problem and

irregular heartbeat) that loaded on different factors in the Gulf and non-Gulf veterans. Sudden loss of strength is not considered in the cluster of symptoms because it loads in the non-Gulf group as well as the Gulf group. With the possibility that these four symptoms comprised a syndrome unique to veterans deployed to the Gulf, we defined a suspected case as a veteran reporting mild or severe problems on all of the four symptoms. A total of 277 (2.4%) of the deployed veterans met this case definition. Although a factor containing the four symptoms was not present for the non-Gulf veterans, there were also 43 (0.45%) non-Gulf veterans with all four complaints. The possible impact of this syndrome is suggested by the presence of at least 3 of the 4 symptoms in 877 (7.7%) of the Gulf veterans compared to 175 (1.8%) of the non-Gulf veterans.

#### Overlap with Other Symptom Based Diagnoses

There were significant overlaps between the suspected cases and PTSD. A total of 191 suspected cases (69%) also met the criteria for PTSD. Conversely, among those who met the criteria for PTSD, 10.7% also reported all of the four symptoms. Anyone who scored 50 or higher on the PTSD checklist was considered as having current PTSD. The suspected cases were almost entirely separated from the veterans with chronic fatigue syndrome. Only 12 of suspected cases (4%) also met the modified 1994 CDC criteria for chronic fatigue syndrome.<sup>26</sup>

#### Demographic and Military Characteristics of Suspected Cases

Relative to the 6730 Gulf War veteran respondents without any of the four symptoms (controls), the 277 suspected cases were more likely to be female (21.7% vs.

15.4%) Army (81.2% vs. 56.8%), minority (39.4% vs. 22.4%), enlisted (94.6% vs. 83.7%) personnel who served in reserve/National Guard units (70% vs. 60.8%) and more likely to be no longer on active duty military service (84.1% vs. 78.7%).

#### Self-reported Exposures

The 277 Gulf War veterans who had all of the four symptoms (suspected cases) reported exposure to a number of potential risk characteristics at a three or more times higher rate than other Gulf War veteran respondents without any of the four symptoms. Table 4 lists exposure variables with a prevalence rate at least three times higher among suspected cases compared to Gulf War veteran controls. The exposures which occurred in more than 50 percent of the suspected cases included eating food contaminated with oil, smoke, or other chemicals; exposure to paint, solvents or petrochemical substances as well as to CARC (Chemical Agent Resistant Compound) paint; and bathing or drinking water contaminated with smoke, oil and other chemicals. Anthrax vaccine was reported to have been received by 55.8% of the suspected cases and 35.6% of the control veterans, and pyrodostigmine bromide pills were ingested by 69.0% of the suspected cases and 43.1% of the controls.

#### Self-reported Medical Conditions

The 277 suspected cases experienced a variety of medical conditions at significantly higher rates ( $p<.0001$ ) than the control group of 6370 who did not complain of any one of the four symptoms (Table 5). Chief among these conditions were diarrhea, migraines, lumbago, hypertension, and tachycardia. The fifty-five fold excess

reporting of seizures, convulsions and blackouts and the 19-fold excess reporting of neuralgia by the cases in comparison to controls were noteworthy.

#### IV. DISCUSSION

Our study differs from those of Haley et al and Fukuda et al in that it is a population based study. We also included a comparison group of non-Gulf veterans. Haley et al study evaluated a small number of Gulf veterans (N=249) from a single Naval reserve unit without non-Gulf war veterans against which to compare the factor structure. All study subjects included in the Fukuda et al. study were members of a U.S. Air Force, Air Force Reserve or Air National Guard unit. They were still on active duty service in the military at the time of the study in 1995. The military experience and other exposure potentials in the Gulf for the Navy or the Air Force personnel might have been substantially and materially different from those who served in the Army and the Marine Corps, which contributed almost  $\frac{2}{3}$  of the deployed troops. Furthermore the health status of those who remained in the military service, less than a third of deployed troops by 1995, would have been different from those who were separated from the military. In contrast, our study included a large number of troops from all four branches of service, all three unit components, those who were on active duty and those who were separated from the military.

Ismail et al study is similar to our study in the study design but different from ours in the statistical analyses. Both studies are based on population based cross-sectional sampling for the study subjects and included both deployed and non-deployed troops.

However, in the U.K. study, only the first three factors were included in the analyses. Just as was described in the U.K. study, we also observed that the Gulf and non-Gulf veterans displayed virtually identical factor solutions in the five factor analysis. Only the six-factor solution model produced different results for the Gulf and non-Gulf veterans.

Our study is limited by the fact that the cluster of four symptoms identified as a neurologic factor is based on the self reported data. These data may be subject to reporting or recall bias. Other limitations of the study include a differential participation rate between Gulf (75.1%) and non-Gulf veterans (64.1%). The demographic and military characteristics of non-participants were similar between Gulf and non-Gulf veterans. The perceived general health status of veterans who responded earlier in the survey did not differ from the veterans who chose to respond toward the end of study period. However, the extent to which ill (or healthy) veterans were under (or over) represented could influence the results.

While the six factors are moderately coherent, there are several overlapping symptoms. For example, two of the fatigue questions load on the "Fatigue/Depression" factor, but also on the "Neurological" factor in the Gulf or non-Gulf sample. This would be consistent perhaps with damage to the peripheral nerves and skeletal muscles. There are undoubtedly a variety of illnesses and conditions, as well as measurement biases, which would tend to result in certain symptoms being related to more than one factor. Notwithstanding these limitations, the important observation of the study is that for the first time, a factor consisting of four symptoms unique to Gulf veterans was identified. Moreover, the Gulf veterans who reported all of the four symptoms were significantly different from other Gulf veterans with respect to reporting of chronic

illnesses, exposure in the Gulf theater, and demographic and military characteristics.

The neurologic factor identified in the study needs to be replicated by other studies of Gulf War veterans. Also, it requires validation through clinical examinations in which standardized objective testing can be performed on the suspected cases and on controls.

In summary, a unique factor consisting of blurred vision, loss of balance/dizziness, speech difficulty and tremor/shaking was found in deployed Gulf War veterans. A group of 277 Gulf veterans who had all of the four symptoms also reported exposures to a number of putative risk factors at a three or more times higher rate than that of other Gulf veterans. A number of associated medical conditions were reported significantly more often by these Gulf veterans than other Gulf veterans. Although a factor by itself does not constitute a disease syndrome, the study finding suggests a possible syndrome related to Gulf War deployment. This result requires strong objective supporting clinical evidence.

Table 1. Distribution of Gulf War Veterans and non-Gulf War Veterans by Gender and Unit Component \*

Unit Component	Gender		
	Male	Female	Total
Active (Regular)	4,800	1,200	6,000
Reserve	4,000	1,000	5,000
National Guard	3,200	800	4,000
Total	12,000	3,000	15,000

\* The target numbers were identical for Gulf war and non-Gulf War veterans.

Table 2. Percent Distribution of Selected Characteristics of Those Who Responded vs. Those Who Have Not Responded

Characteristics	Phase I Respondents (N=15,817)	Phase II Respondents (N=5,100)	Non Respondents (N=9,083)
<b>Sex</b>			
Male	79.3	81.8	80.3
Female	20.7	18.2	19.7
<b>Age (Mean Age In 1991) Years</b>	31.6	29.2	27.7
<b>Race</b>			
White	76.0	69.2	57.4
Black	16.4	24.2	32.8
Other	7.6	6.6	9.8
<b>Marital Status</b>			
Married	55.2	50.3	2.4
Single	39.4	44.7	53.5
Other	5.4	5.0	4.1
<b>Rank</b>			
Enlisted	82.6	88.0	92.4
Officer	15.8	11.0	7.0
Warrant	1.5	1.0	0.6
<b>Branch</b>			
Air Force	12.9	12.8	8.6
Army	63.8	61.7	65.7
Marine	10.6	12.3	11.7
Navy	12.7	13.2	14.0
<b>Unit Component</b>			
Active	38.1	40.3	43.2
National Guard	27.8	26.7	24.7
Reserve	34.1	33.0	32.1
<b>Current Active Duty</b>			
Yes	20.3	16.2	-----
No	79.7	83.8	-----

Table 3. Summary of Factor Analyses for Symptoms Reported by Gulf War Veterans and Non-Gulf Veterans

Description of Symptoms	Factor Loading <sup>a</sup>	
	Gulf (N=10,423)	Non-Gulf (N=8,960)
<b>Factor 1: Fatigue/Depression</b>		
Awaken tired and worn out	85	59
Concentration and memory problems <sup>b</sup>	49	55
Excessive Fatigue	62	22
Fatigue >24 h after exertion	49	14
Feeling anxious, irritable, or upset	63	78
Feeling depressed or blue	56	79
Sleep difficulty	58	54
Sleepiness during daytime	74	45
<b>Factor 2 : Neurological</b>		
Blurred vision	32	13
Concentration/memory problems <sup>b</sup>	38	19
Irregular heartbeat <sup>c</sup>	32	8
Loss of balance/dizziness	42	25
Speech difficulty	49	16
Sudden loss of strength	41	51
Tremors/shaking	40	16
Excessive fatigue <sup>d</sup>	14	62
Fatigue>24 h after exertion <sup>e</sup>	65	63
<b>Factor 3: Musculoskeletal/Rheumatologic</b>		
Back pain/spasms	34	43
Generalized muscle aches	56	54
Joint aches	79	78
Numbness in hands/feet	44	50
Swelling in joints	65	63
Swelling in extremities	46	41
<b>Factor 4: Gastrointestinal</b>		
Constipation	32	20
Diarrhea	48	45
Nausea	80	79
Reflux, heartburn, indigestion	33	23
Stomach/abdominal pain	55	40
Vomiting	72	74
<b>Factor 5 : Pulmonary</b>		
Coughing <sup>f</sup>	29	30
Irregular heartbeat <sup>g</sup>	30	32
Shortness of breath	82	75
Tightness in chest	70	63
Wheezing	64	68
<b>Factor 6: Upper respiratory</b>		
Coughing <sup>h</sup>	39	41
Runny nose	28	40
Sore throat	74	76
Swollen glands	42	45
Trouble swallowing	55	55

<sup>a</sup> factor loading times 100

<sup>b</sup> also loads on factor 2, loadings are 38 Gulf, 19 non-Gulf

<sup>c</sup> also loads on factor 1; loadings are 49 Gulf, 55 non-Gulf

<sup>d</sup> also loads on factor 5; loadings are 30 Gulf, 32 non-Gulf

<sup>e</sup> also loads on factor 1; loadings are 62 Gulf, 22 non-Gulf

<sup>f</sup> also loads on factor 1; loadings are 49 Gulf, 14 non-Gulf

<sup>g</sup> also loads on factor 6, loadings are 39 Gulf, 41 non-Gulf

<sup>h</sup> also loads on factor 2, loadings are 32 Gulf, 08 non-Gulf

<sup>h</sup> also loads on factor 5, loadings are 29 Gulf, 30 non-Gulf

Table 4. Selected Self-Reported Exposure in Gulf Theater for Cases and Comparison Groups

Exposure	Cases (N=277)	Controls (N=6730)	All Respondents (N=11,441)
CARC Paint	51.2	16.3	21.7
Depleted Uranium	28.9	6.6	9.5
Nerve Gas	42.3	4.6	9.6
Ate Food Contaminated with Oil, Smoke	73.4	20.6	30.2
Bathed in or Drank Contaminated Water	59.8	19.1	28.1
Sexual Assault	3.3	0.4	0.8
Sexual Harassment	15.0	2.6	5.1
Other Harmful Exposure	56.6	18.1	25.6
Botulism Vaccine	26.3	9.2	12.5

Cases and Control groups significantly different, p<.0001 for all variables

Table 5. Percent Distribution of Selected Medical Conditions for Cases and Comparison Groups

Medical Conditions	Cases (N=277)	Controls (N=6730)	All Respondents (N=11,441)
Back disorder	48.9	9.3	15.4
Disease of muscles or tendons	34.1	4.6	8.5
Enteritis	28.5	4.8	8.1
Diarrhea	67.3	13.6	23.4
Migraines	51.1	10.8	18.5
Neuralgia or neuritis (Nerve inflammation)	32.1	1.7	5.0
Hypertension	46.7	7.7	12.9
Tachycardia	45.6	3.7	9.6
Bronchitis	33.7	8.7	13.4
Repeated seizures, convulsions or blackouts	22.2	0.4	2.6

Cases and Control groups significantly different, p<.0001 for all variables

**Table 6. Summary of Four Studies Which Used Factor Analysis**

Authors	Target Population	Response Rate	Sample Size	Summary of Factor
Haley et al	one US Navy reserve construction unit Gulf War veterans	41%	249	1. impaired cognition 2. confusion-ataxia 3. arthromyoneuropathy 4. phobia- apraxia 5. fever-adenopathy 6. weakness-incontinence
Fukuda et al	two Air National Guard Units in Pennsylvania and one Air Force Reserve unit and one active duty Air Force unit in Florida	35%-73%	3723	1. mood-fatigue-cognition 2. musculoskeletal
Ismail et al	random sample of three UK male veteran populations Gulf, Bosnia, Era cohorts system	65%	8195	1. mood cognition 2. respiratory system 3. peripheral nervous
This Study	stratified random sample of population based Gulf and non-Gulf veterans	70%	20,917	1. fatigue/depression 2. neurological (Gulf veterans only) 3. musculoskeletal/ rheumatologic 4. gastrointestinal 5. pulmonary 6. upper respiratory

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